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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/784,222	10/28/91	WESTBROOK C	ARCO:010/UCH

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EXAMINER	
REES,D	

ART UNIT	PAPER NUMBER
1807	29

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 07/784,222	Applicant(s) Westbrook
	Examiner Dianne Rees	Group Art Unit 1807

☒ Responsive to communication(s) filed on *Aug 22, 1997*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-3 and 5-34* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3 and 5-34* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Withdrawal of Finality of Last Office Action Transitional Application under 37 CFR 1.129 (a):

Since this Application is eligible for the transitional procedure of 37 CFR 1.129 (a) and the fee set forth in 37 CFR 1.17 (r) has been timely paid,the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.129 (a). Applicant's first submission filed on 8/22/97 has been entered.

Claim Rejections - 35 USC § 112

1. Claims 1-3, 5-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following phrases render the claims vague and indefinite:

Claim 1 is indefinite in the recitation of "a hybridization site" as it is unclear if the site is within the gene or if the claim can encompass hybridization sites within RNA transcripts resulting from the translocation. The claim might be amended to recite --a hybridization site for the first probe within the BCR gene-- and a --hybridization site for the second probe within the ABL

gene--. See also claim 34 and this rejection is applied to claim 34 as well over the use of this language.

Claim 5 is indefinite in that it depends on a canceled claim (and therefore claims 6-7 also ultimately depend on a canceled claim).

Claims 21-23 are indefinite in the recitation of "as illustrated" as it is unclear what particular detail is being referred to in the figure. It is suggested that the term "as illustrated in..." be deleted in claims 22-23 as the meaning of the "first exon. of the BCR gene" and the" last exon. of the ABL gene" would be understood to those of ordinary skill in the art. Claim 21 is additionally indefinite , however, in the recitation of the "5' region" as it is unclear what the metes and bounds of the 5' region is or what number of bases this encompasses 5' to the major breakpoint cluster region. It is acknowledged that those of skill in the art would understand that the major breakpoint cluster region is defined by a specific type of DNA sequence rearrangement, however it is unclear how much sequence 5' to the breakpoint is actually being included by the claim.

Claim 29 is indefinite in that it is unclear what the metes and bounds of the "control probe" is as it is unclear what the control probe is controlling for.

Claim 33 is indefinite in that it is unclear how a breakpoint can be diagnostic or prognostic of ALL and CML since different rearrangements lead to each disease. Does applicant intend that the probes are capable of detecting both ALL and CML?

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 1,2, 8, 9, 10, 12, 13, 14, 15,17-20, 21,22,29, 30,31,32, and 34 are rejected under 35 U.S.C. 102(e) as being anticipated by Kawasaki et al (USPAT 5057410, filed Aug 5, 1988).

Kawasaki et al. (USPAT 5057410, Oct 15, 1991) teaches a method for the detection of RNA such as resulting from chromosomal translocations, including bcr-abl translocations, using the polymerase chain reaction. Compositions including two oligonucleotide primers are taught; the first being complenentary with sequences of cDNA that are on the 3' side of the bcr-abl exon.-exon.. junction, and the second being homologous with sequences that are on the 5' side of the

exon.-exon. junction. (See column 8, and column 11, lines 10-70). Primers are taught as being used which are hybridized to a first exon at the 5' end of the chimeric mRNA (for example, in the cases of bcr-abl translocations, the first exon. of bcr) and the second primer is taught as being complementary to a second exon. (such as exon. II of ABL)(see column 4, "summary") . Kawasaki et al. teaches that primers may be labeled using biotin.Since the PCR product amplified by the primers approximately 246 bases (see Figure 2), it is interpreted that a hybridization site for the first primer and the second primer are brought within approximately 800 kb of each other by said chromosomal translocation. Kawasaki et al also teaches that different kinds of BCR primers may be used to distinguish between those rearrangements that juxtapose either BCR exons 1,2,or 3 (i.e allowing one to distinguish between the translocation resulting in the production of p210 vs p190) (see column 11, lines 31-50). Kawasaki et al teaches that that any one the primer pair combinations might be used which hybridizes to BCR exon. 1 and ABL exon. II, one which hybridizes to BCR exon. 2, and ABL exon. II and one which hybridizes to BCR exon. 3, and ABL exon. II. Kits are thus taught which comprise the three types of BCR primers and one type of ABL primer. (It is noted that the use of the term comprising in the instant kit claims do not exclude the addition of additional probe/primers.)As the features taught by Kawasaki for the above primers are indistinguishable over the recited features of the probes in the instant claims ; the primers taught by Kawasaki anticipate the claimed composition of probes. Claims 8-10, 17-20, add limitations that refer only to the intended use of the probes and are therefore also anticipated by the teachings of Kawasaki. The primers/probes of Kawasaki

inherently hybridize to hybridization sites brought together by a translocation wiht breakpoints on the long arms f human chromosomes and 22, specifically t(9:22)(q11;34) (as recited in claims 12 and 13)(see column 2, lines 54-70). The probes/primers taught by Kawaksaki are diagnostic of ALL and CML(column 4, lies 6-70).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1,2, 8-12,14, 17-20,22, 23,29, 31, 34 are rejected under 35 U.S.C. § 103 as being unpatentable over Stephenson et al (USPAT 4681840, 1987).

Stephenson et al. teaches synthetic oligonucleotides that are useful in the diagnosis of CML, teaching probes that are complementary to the two most common bcr-abl splice sites. Synthetic oligonucleotides are taught that are complementary to a sequence in bcr exon. 2 and a

sequence in abl exon. 2. Thus the sequences are capable of hybridizing to sequences that are ABL nucleic acid flanking sequences and BCR nucleic acid flanking sequences and are capable of detecting the p210 fusion gene. The probes/primers are capable of hybridizing to sequences that are at least approximately 800kb apart in the aberrant chromosome. The probes inherently possess the property of being capable of hybridizing (at least to some extent) with chromosomal DNA in situ in cells such as those which might be in interphase. The probes hybridize to the 5' "region" of chromosome 22, to a portion of the first exon. and the 3' "end" of the abl gene. (See column 10 and Figure 1).The limitations of claims 17-20 are also met as the composition is defined in terms of its structural properties regardless of where a sample which it *might* be used to assay *might* be obtained.Stephenson further teaches Bam HI fragments which are capable of hybridizing to the first exon. in BCR as well as a Bam fragment that is capable of hybridizing with at least a part of the last exon. of the ABL gene (see Figure 1).

Stephenson does not teach providing a composition which includes a pair of probes , the teachings of labelled probes or the teaching that the probes are provided in a kit However it would have been prima facie obvious to put multiple probes in a kit, including a combination of two, or three, or four, et c, for the expected benefit of providing the experimenter with the choice of probes to use to detect the bcr, and abl oncogenes. Further the labeling of probes, for example with 32P ,was well known in the art at the time that the invention was made as was the convention of including compositions useful to perform a method in a kit, in order to provide such benefits of standardized, preweighed reagents in a convenient format. It therefore would have

been prima facie obvious to one of ordinary skill in the art at the time that the invention was made to label the probes, for use in Southern analysis for example, or to provide the probes in a kit format to capitalize on the advantages that such a format provides. Applicant is reminded that as these are products claims, the motivation to assemble the products need not be the same as those of applicant's; it is acknowledged that Stephenson does not envision the use of dual labeled probes to detect bcr-abl in a single assay; however there is a credible motivation to assemble compositions of multiple numbers of probes, including two, given the teachings of Stephenson, the motivation to do so to have a choice of probes to use in single probe assays.

Claims 5-7 were not included in the above rejections as they depended upon a canceled claim. However, it is noted that if Applicant corrects the dependency of claim 5 to include claim 1, that the Examiner would consider the use of fluorescent labeled probes/primers to be obvious over the teachings of either Kawasaki et al. or Stephenson et al. As one would be motivated to label the probes/primers of the references with any of the types of labels known in the art at the time that the invention was made, including fluorescent probes as one would expect these labels to provide equivalent results -a means of detection of the hybridization products obtained.

Claims 3,4,16,24-28 are allowable over the art as the art does not teach or fairly suggest providing dual labeled probes or primers, or the specific probes recited in the claims. The claims

would be allowable subject to overcoming 112 second rejections above and if rewritten as independent claims.

No claims are allowed.

Response to Applicant's arguments:

Applicant's amendments and arguments have over come rejections previously made under 35 USC 112 first paragraph and these rejections are withdrawn.

Rejections of claims made previously under 35 USC 112 second paragraph are withdrawn in view of Applicant's amendments. However, Applicant's amendments have necessitated a new grounds of rejection under 35 USC 112 second paragraph as discussed above.

A new grounds of rejection has been raised under 35 USC 102(e) and 103. However, some of Applicant's arguments as they are relevant to the newly applied rejections are discussed here.

Applicant's invention is the discovery of hybridization conditions and types of probes necessary for the dual labeling of chromosomes involved in translocations in situ. The hybridization sites must be approximately within 800 bases of each other to provide resolvable doublets under the microscope. However, Applicant's claims in the instant application are drawn to compositions for use in the method. As discussed above, and reiterated here, one does not require the same

motivation as Applicant to provide the compositions and kits recited in the claims Dual labeled probes were not anticipated or suggested by the art (since translocations were either detected using single probes (as in Stephenson) to detect bands on a gel, or double probes (as in Kawasaki) to detect a single amplification products, there was no motivation in the art at the time of filing to label the PCR primers of Kawasaki with two distinguishable labels or to provide hybridization probes with two distinguishable labels. However there was motivation to provide pairs of probes, either unlabeled, or labelled with a single type of label, together that hybridize to hybridization sites within approximately 800 bases as these would be useable in PCR amplification reactions (as taught by Kawasaki) or to provide one with a choice of different probes to use in a hybridization assay such as taught by Stephenson. There was further ample motivation to provide a genetic probe that was capable of hybridizing to the first exon. of BCR or to at least a part of the last exon. of the ABL gene (as recited in claims 22 and 23). The Examiner further respectfully disagrees that the probes of Stephenson are not capable of hybridizing to the first exon. of BCR or the last exon. of ABL as Stephenson teaches a number of cloned fragments, in addition to those which hybridize to the second exons of BCR and ABL, including those which are capable of hybridizing to the first exon. of BCR and last exon. of ABL (see Figure 1).

Papers related to this application may be submitted to Group 1800 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Official Communications are (703) 305-3014 and (703) 305-4227. Please note that the faxing of such

papers must conform with the notice to Comply published in the Official Gazette, 1096 OG 30 (Nov 15, 1989). Applicant is informed that all Official communications that go through the Fax Center will not be forwarded directly to the Examiner but will be routed through docketing. Applicant is encouraged to clearly mark any communications to the Office as DRAFT, OFFICIAL (and further as RESPONSE TO OFFICE ACTION, or AFTER FINAL. etc.) For any inquiries concerning the status of of a Faxed Communication please contact (703) 308-9378.

An inquiry regarding the Office Action should be directed to examiner Dianne Rees, Ph.D., whose telephone number is (703) 308-6565. If Applicant does not receive a complete office action or references, please contact Michelle Richardson , whose telephone number is (703) 308-4309. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Calls of a general nature may be directed to the Group receptionist who may be reached at (703) 308-0196.

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12/7/97

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